The thalassemias and health care in Canada: a place for genetics in medicine

David H.K. Chui, MD, FRCPC; Shiu C. Wong, PhD; Charles R. Scriver, OC, MD, FRSC

There is good evidence that genetic disorders play an important role in human disease.[1] There are over 4000 Mendelian (single-gene) disorders, and up to 60% of Canadians will experience a disease with a significant genetic component in their lifetime.[2] Canada has been a leader in taking the initiative to apply the principles of genetic screening in the health care system.[3] The main targets are phenylketonuria and other inborn errors of metabolism, congenital hypothyroidism, Tay-Sachs disease, sickle cell disease, the thalassemias and Down's syndrome. Each is reached through a population "window" such as newborn infants in nurseries, students in high schools and adults during their reproductive years.

The thalassemia syndromes are of particular interest for two reasons. First, they constitute the most common single-gene disease in the world; they are found mainly in regions where malaria has been or still is endemic. Second, migration of people from areas where thalassemia is relatively common brings the genes and their associated diseases to regions where they were previously unknown, such as one of the oldest European settlements in Canada.[4] In recent years the Canadian population has increasingly included people with African, Asian, Hispanic, Mediterranean or Middle Eastern ancestry, in whom the gene frequency for thalassemia is relatively high. The associated disease burden in the population is already substantial and is likely to increase.

Consequently, it is relevant for health care professionals, particularly family physicians, obstetricians and pediatricians, to be familiar with the thalassemias, to know that they can be diagnosed early in pregnancy and to know that patients can have access to sophisticated diagnostic and treatment programs in most Canadian urban centres. In addition, comprehensive and coordinated programs need to be developed for public education, carrier detection, genetic counselling, prenatal diagnosis and treatment to provide the standard of care to be expected in a country like Canada. These programs would furnish the affected couples with all the pertinent information so that they can make a decision best suited to them and their offspring.

What is thalassemia?

Adult hemoglobin, HbA, is a tetramer of two α-globin and two β-globin chains ($\alpha_2\beta_2$), each of which contains a heme group. The other two minor hemoglobins in adults are HbA_2 ($\alpha_2\delta_2$) and HbF ($\alpha_2\gamma_2$). Alpha-globin chains are coded for by two adjacent α-globin genes on the short arm of chromosome 16. Beta-globin chains are coded for by a single β-globin gene on the short arm of chromosome 11.

The thalassemias are hereditary disorders due to mutations in either α-globin or β-globin genes.[5] These mutations cause decreased or absent production of α-globin or β-globin chains. In general, α-thalassemia is due to the deletion of one or more of the four normal α-globin genes.[6] On the other hand, β-thalassemia is usually caused by point mutations or by mutations involving small insertions or

Dr. Chui is director of the Provincial Hemoglobinopathy DNA Diagnostic Laboratory and is professor of pathology at McMaster University, Hamilton, Ont.; Dr. Wong is with the departments of Laboratory Medicine and Medicine, Foothills Provinicial General Hospital and the University of Calgary, Calgary, Alta.; and Dr. Scriver is with the de Belle Laboratory for Biochemical Genetics, McGill University-Montreal Children's Hospital Research Institute, and the Department of Pediatrics and the Centre for Human Genetics, McGill University, Montreal, Que.

Reprint requests to: Dr. David H.K. Chui, Department of Pathology, McMaster University Medical Centre, 1200 Main St. W, Hamilton, ON L8N 3Z5

deletions in the β-globin gene. More than 90 such β-thalassemia mutations are known worldwide.[7]

People who are heterozygous for either form of thalassemia may have mild hypochromic microcytic anemia but are otherwise healthy and asymptomatic. However, a fetus with homozygous α-thalassemia due to deletion of all four normal α-globin genes is usually stillborn during the third trimester of pregnancy or dies shortly after birth. In addition, the pregnancy carries an increased risk of serious maternal complications, such as pre-eclampsia and antepartum and postpartum hemorrhage.

Infants who are homozygous for β-thalassemia (β-thalassemia major) are normal at birth but usually manifest severe anemia within a few months and thereafter require transfusions at regular intervals and iron chelation therapy.[8-11] Remarkable progress has been made in recent years in the care of these children and of young adults so afflicted. Nevertheless, their life expectancy is currently estimated to be, at best, 30 to 35 years. Transplantation of bone marrow from HLA-identical sibling donors is reported to be an effective therapy, but the procedure has a mortality rate of 18%.[12] Moreover, finding matched donors is not always possible. Somatic cell gene therapy is being actively investigated as a cure for thalassemia.

People can inherit a combination of α-thalassemia and β-thalassemia with or without other mutant globin genes, with consequences for health.[13,14] Those who have inherited both β-thalassemia mutations and sickle cell hemoglobin mutations may show a clinical picture similar to that of patients who have homozygous sickle cell disease with vaso-occlusive episodes. People who have inherited both β-thalassemia and HbE mutations have severe anemia similar to that of patients with β-thalassemia major.

Screening programs

The major consequences of thalassemia can be avoided if the population at risk and the individuals within it who are particularly affected understand the problem. A comprehensive program encompassing public education, screening for carriers, genetic counselling and prenatal diagnosis has markedly reduced the incidence of β-thalassemia major in some Mediterranean regions, such as Sardinia, with a very significant impact on the health care of the population.[15-17] These programs do not add significant costs to the health care system.[15,16,18,19]

Within the Canadian populations in which the gene frequency for thalassemia is known to be relatively high it is reasonable to screen for carriers among people of reproductive age, particularly couples who are planning a family and women who have recently conceived or are in the early stages of pregnancy. Relatives of patients with β-thalassemia major and relatives of thalassemia carriers should also be screened. Screening programs for the population at large are presently available only in Montreal,[17] despite the presence of large communities at risk elsewhere in Canada.

The significant laboratory findings in people heterozygous for α- or β-thalassemia are erythrocyte hypochromia and microcytosis (mean corpuscular volume of less than 80 fL), with or without mild anemia. The serum ferritin level should be determined in order to rule out iron deficiency. Hemoglobin electrophoresis should also be performed. In most instances an elevated HbA_2 or HbF level, or both, indicates a β-thalassemia carrier state. The diagnosis of an α-thalassemia carrier state is suggested by normal HbA_2 and HbF levels and the presence of HbH inclusion bodies in the erythrocytes. The development of more specific and sensitive screening tests for the α-thalassemia carrier state is in progress.[20] Laboratory diagnosis of both carrier states is available in major hospitals throughout Canada.

If one partner is found to be a thalassemia carrier the other partner can be counselled and tested. If both partners are carriers there is a 25% chance during each pregnancy that the fetus will inherit both parents' thalassemic mutations. Once identified such couples can receive counselling and information about the maternal and child health services available. If prenatal diagnosis is contemplated or desired the first step is to determine the thalassemia mutations of each partner by DNA analysis. There are hemoglobinopathy DNA diagnostic laboratories in Calgary, Hamilton and Montreal. These facilities also provide prenatal diagnosis of the thalassemias through the use of fetal cells obtained from either chorionic villus sampling in the first trimester or amniocentesis in the second trimester of pregnancy.

Conclusions

Molecular biology has provided valuable information about the human globin genes and their mutations. This knowledge is being transferred to clinical practice in many centres, and people at risk for thalassemia are the beneficiaries. Health care professionals should be aware that thalassemia is now a Canadian disease and that appropriate screening and diagnostic tests are available.

On the whole the Canadian health care system has not recently kept pace with advances in genetics: the services described here are not universally available, although they have been well accepted by the communities at risk in Montreal. Medical genetics

belongs in the health care system, and it should be given due consideration in the clinic and in the office. Prevention of the thalassemias, a specific example of "genetics in medicine", presents a still unmet challenge in the Canadian health care system.

References

1. Scriver CR: Human genes: determinants of sick populations and sick patients. *Can J Public Health* 1988; 79: 222-224
2. Baird PA, Anderson TW, Newcombe HB et al: Genetic disorders in children and young adults: a population study. *Am J Hum Genet* 1988; 42: 677-693
3. *Genetic Screening. Programs, Principles, and Research*, National Academy of Sciences (National Research Council), Washington, DC, 1975
4. Kaplan F, Kokotsis G, De Braekeleer M et al: β-thalassemia genes in French-Canadians: haplotype and mutation analysis of Portneuf chromosomes. *Am J Hum Genet* 1990; 46: 126-132
5. Weatherall DJ, Clegg JB, Higgs DR et al: Thalassemia. In Scriver CR, Beaudet AL, Sly WS et al (eds): *The Metabolic Basis of Inherited Disease*, 6th ed, McGraw, Toronto, 1989: 2305-2332
6. Higgs DR, Vickers MA, Wilkie AOM et al: A review of the molecular genetics of the human α-globin gene cluster. *Blood* 1989; 73: 1081-1104
7. Kazazian HH Jr: The thalassemia syndromes: molecular basis and prenatal diagnosis in 1990. *Semin Hematol* 1990; 27: 209-228
8. Olivieri NF, Buncic JR, Chew E et al: Visual and auditory neurotoxicity in patients receiving subcutaneous deferoxamine infusions. *N Engl J Med* 1986; 314: 869-873
9. Olivieri NF, Koren G, St. Louis P et al: Studies of the oral chelator, 1,2-dimethyl-3-hydroxypyrid-4-one in thalassemia patients. *Semin Hematol* 1990; 27: 101-104
10. Bronspiegel-Weintrob N, Olivieri NF, Tyler B et al: Effect of age at the start of iron chelation therapy on gonadal function in β-thalassemia major. *N Engl J Med* 1990; 323: 713-719
11. Fosburg MT, Nathan DG: Treatment of Cooley's anemia. *Blood* 1990; 76: 435-444
12. Lucarelli G, Galimberti M, Polchi P et al: Bone marrow transplantation in patients with thalassemia. *N Engl J Med* 1990; 322: 417-421
13. Akerman BR, Fujiwara TM, Lancaster GA et al: Identification of deletion and triple α-globin gene haplotypes in the Montreal β-thalassemia screening program: implications for genetic medicine. *Am J Med Genet* 1990; 36: 76-84
14. Chui DHK, Patterson M, Dowling CE et al: Hemoglobin Bart's disease in an Italian boy — interaction between α-thalassemia and hereditary persistence of fetal hemoglobin. *N Engl J Med* 1990; 323: 179-182
15. Community control of hereditary anaemias: memorandum from a WHO meeting. *Bull WHO* 1983; 61: 63-80
16. Cao A, Rosatelli C, Galanello R et al: The prevention of thalassemia in Sardinia. *Clin Genet* 1989; 36: 277-285
17. Scriver CR, Bardanis M, Cartier L et al: β-thalassemia disease prevention: genetic medicine applied. *Am J Hum Genet* 1984; 36: 1024-1038
18. Ostrowsky JT, Lippman A, Scriver CR: Cost-benefit analysis of a thalassemia disease prevention program. *Am J Public Health* 1985; 75: 732-736
19. Prenatal diagnosis and genetic screening: community and service implications. Summary and recommendations of a report of the Royal College of Physicians. *J R Coll Physicians Lond* 1989; 23: 215-220
20. Chui DHK, Wong SC, Chung S-W et al: Embryonic ζ-globin chains in adults: a marker for α-thalassemia-1 haplotype due to a > 17.5 kb deletion. *N Engl J Med* 1986; 314: 76-79

Conferences

continued from page 20

Jan. 31-Feb. 1, 1991: Leadership Strategies for Health Care Managers
Bristol Place Hotel, Toronto
Conference and Seminar Services, Humber College, 205 Humber College Blvd., Etobicoke, ON M9W 5L7; (416) 675-5077, FAX (416) 675-0135

Feb. 1-2, 1991: Sport Med '91 (sponsored by the Ontario Medical Association's section on sports medicine)
Prince Hotel, Toronto
Dr. Janet Ames, program chairman, Sport Med '91, 600-250 Bloor St. E, Toronto, ON M4W 3P8; (416) 963-9383

Feb. 7-9, 1991: Conference on Medicine and the Humanities
Dalhousie Medical School, Halifax
Professor June Penney, Office of the Dean, Faculty of Medicine, Sir Charles Tupper Medical Building, Dalhousie University, Halifax, NS B3H 4H7; (902) 494-3400

Feb. 19-20, 1991: Advanced Cardiac Arrhythmia Interpretation
Ramada Airport West, Mississauga, Ont.
Conference and Seminar Services, Humber College, 205 Humber College Blvd., Etobicoke, ON M9W 5L7; (416) 675-5077, FAX (416) 675-0135

Feb. 21-22, 1991: Basic Cardiac Arrhythmia Interpretation
Ramada Airport West, Mississauga, Ont.
Conference and Seminar Services, Humber College, 205 Humber College Blvd., Etobicoke, ON M9W 5L7; (416) 675-5077, FAX (416) 675-0135

Feb. 21-24, 1991: Pan-American Doctors' Club (Canadian section) 45th Meeting
Manzanillo, Mexico
Dr. Donald P. Hill, vice-president, Medical Affairs, Continuing Medical Education, Ottawa General Hospital, 501 Smyth Rd., Ottawa, ON K1H 8L6; (613) 737-8455

Feb. 25-26, 1991: 12 Lead ECG Interpretation
Ramada Airport West, Mississauga, Ont.
Conference and Seminar Services, Humber College, 205 Humber College Blvd., Etobicoke, ON M9W 5L7; (416) 675-5077, FAX (416) 675-0135

Feb. 25-Mar. 1, 1991: College of Family Physicians of Canada (Alberta Chapter) 36th Annual Scientific Assembly
Banff Park Lodge, Banff, Alta.
Mrs. E. Taschuk, administrative secretary, Alberta Chapter, College of Family Physicians of Canada, PO Box 3846, Stn. D, Edmonton, AB T5L 4K1; (403) 456-1518

continued on page 39